UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/070,629	04/30/1998	PETER PALESE	6923-071-999	4644

7590 01/14/2003

PENNIE & EDMONDS
1155 AVENUE OF THE AMERICAS
NEW YORK, NY 100362711

EXAMINER
SCHEINER, LAURIE A

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 01/14/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/070,629	Applicant(s) Palese et al.
	Examiner Laurie Scheiner	Art Unit 1648

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 15, 2002*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1 and 30-54* is/are pending in the application.

4a) Of the above, claim(s) *30-54* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *21*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 15, 2002 has been entered.

Claims 1 and 30-54 are pending in this application. Claims 30-54 are withdrawn from consideration as not corresponding to claims examined prior to the filing of a request for continued examination. Claim 1 is considered in below.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with the claim. Claim 1 is drawn toward a recombinant influenza virus containing a region which encodes any tumor-associated antigen. Moreover, the recombinant may be admixed with a pharmaceutically acceptable carrier for use as vaccine. It is asserted that the claims as reasonably interpreted could encompass virtually any nucleotide sequence encoding virtually any tumor-associated antigen or epitope, none of which (with the exception of β-*gal*) are adequately supported by the disclosure. Applicants are reminded of the legal considerations governing enablement determinations pertaining to undue experimentation as disclosed in *In re Wands,* 8 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be

considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer,* 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

1) Other than β-*gal,* the disclosure fails to provide adequate guidance pertaining to the structural characteristics of any given TAA sequence. The claim is broadly directed toward any TAA sequence insert. In the absence of further direction pertaining to the generic structural requirements for any given heterologous sequence, the skilled artisan could not reasonably predict the nucleotide sequence which would be responsible for suppressive activity.

2) The disclosure fails to identify the molecular determinants modulating the suppressive activity of any given heterologous TAA sequence. The single β-*gal* identified by applicants fails to provide for structural motifs common with other TAA sequences which would function as claimed. Thus, the skilled artisan has only been extended an undue invitation to further experimentation.

3) The disclosure fails to include a clear, concise, and reproducible method for obtaining TAA with the desired activity commensurate in scope with that which is claimed. The disclosure provides a single preparative method wherein β-*gal* is the single expressed tumor antigen determinant contained within the transfected recombinant influenza A virus. However, none of these limitations are present in the claim language. The structural limitations are so vague and indefinite that they fail to provide a reliable and reproducible method for obtaining a

functional construct. Applicants are directed toward pages 15-22 of the specification for direction in drafting the process limitations.

4) The prior art is unpredictable and fails to provide any guidance pertaining to the generic structural and functional requirements of the influenza recombinant and influenza recombinant containing vaccine. Additionally, the prior art provides cautionary guidance with respect to specific cell lines employed by applicants in their instant *in vitro* experiments. Thus, conclusions drawn in the specification with respect to *in vitro* experiments are not supported by the art. That is, Rao et al. (J. Immunol. **156**:3357-3365, 1996) when discussing applicants' experimental model teach that "[i]t is important to realize that the tumor model system in which these studies were completed is artificial. β-*gal* represents a large xenogeneic Ag introduced into a tumor cell line and tested in syngeneic animals, whereas many of the human TAAs cloned thus far, as well as the mouse Ag PIA, are nonmutated "self" proteins. Thus, the question arises as to whether data derived from the use of such a foreign Ag as a TAA will have relevance to the human situation in which most TAAs appear to be predominantly self Ags. It is worth noting, however, that similar systems, although using foreign proteins as model TAAs, have been instructive, e.g., transfection of the NP gene from vesicular stomatitis virus into EL4 thymoma or transfection of the human carcinoembryonic Ag (CEA) into MC38, a murine adenocarcinoma. Interestingly, the host response to challenge with either CT26.WT or CT25.CL25, expressing β-*gal*, was unaltered, and we found no evidence of systemic immunity elicited to β-*gal*. Both CT26.WT and CT26.CL25 grow equally well and are equally lethal after i.v. injection. Indeed, the β-*gal* model system may be most relevant to human tumors possessing TAAs that originate from viruses, fusion proteins resulting from translocations, or genetic events that result in the expression of foreign proteins arising from mutations, frame-shifts, translation of introns, and the

loss of stop codons." It is noted, however, that applicants' disclosure fails to provide any support of influenza A recombinants containing TAAs that originate from viruses, etc.

Restifo (Current Opinion in Immunology, 1996, **8**:658-663) teaches at page 660 that there are concerns with respect to anti-cancer vaccines which are not yet adequately addressed in animal models. "The first concerns the duration of tumors in humans. Whereas tumor deposits may exist for years in humans before they are treated, or even detected, the time course studied in mice is generally measured in weeks and sometimes even in days. The longer kinetics of the tumor-bearing state could increase the heterogeneity of the tumor cells, resulting in cell to cell differences that include antigen expression and antigen processing and presenting efficiency. Human tumor cells can escape immune recognition by a number mechanisms, including loss of β2-microglobulin, down regulation or loss of the expression of particular HLA class I loci, and down regulation, mutation or deletion of the proteasome component molecules latent membrane proteins -2 and -7 as well as of transporters associated with antigen processing. Prior chemotherapy or radiotherapy could complicate problems related to the mutability of tumor cells. Such mutability can result in powerfully resistant tumor cells when the number of tumor cells are counted in trillions. Furthermore, when tumor weight is measured in kilograms rather than in grams or milligrams, issues of peripheral tolerance as well as other forms of specific and nonspecific immunosuppression could be qualitatively different."

5) The breadth of the claimed invention could conceivably encompass an inordinate number of polynucleotides encoding TAAs, most all are inadequately supported by the disclosure as enumerated above.

6) The disclosure fails to meet the legal requirements dictating that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the

specification. *In re Fisher,* 427 F.2d 833, 839, 166 U.S.P.Q. 18, 24 (C.C.P.A. 1970). *In re Vaeck,* 20 U.S.P.Q.2d 1438 (C.A.F.C. 1991). *In re Angstadt*, 537 F.2d 498, 502-03, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976). The court stated in *In re Vaeck* that "there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed. This means that the disclosure must adequately guide the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility. Where, as here, a claimed genus represents a diverse and relatively poorly understood group of tumor associated antigens, the required level of disclosure will be greater than, for example, the disclosure of an invention involving a "predictable" factor such as a mechanical or electrical element."

In summation, the disclosure fails to provide sufficient guidance pertaining to the molecular determinants modulating the cancer suppressive activity of any given recombinant influenza virus containing sequence encoding any given TAA, the disclosure fails to provide sufficient guidance pertaining to those variants or derivatives that can reasonably be expected to have and retain suppressive activity. Furthermore, the prior art fails to provide sufficient guidance pertaining to the structural requirements of analogous elements. Thus, the skilled artisan could not possibly predict the nucleotide sequence of various functional equivalents. Accordingly, when all the aforementioned factors are considered together, it would clearly require undue experimentation to practice the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laurie Scheiner, whose telephone number is (703) 308-1122. Due to a flexible work schedule, the examiner's hours typically vary each day. However, the examiner

can normally be reached Monday thru Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4027.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

Correspondence related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Official communications should be directed toward one of the following Group 1600 fax numbers: (703) 308-4242, (703) 305-3014, (703) 872-9306 or (703) 872-9307. Informal communications may be submitted directly to the Examiner through the following fax number: (703) 746-5226.

Laurie Scheiner/LAS
January 6, 2003

LAURIE SCHEINER
PRIMARY EXAMINER